REMARKS

Claims 1 to 35, 38 to 41, and 71 to 111 are in the application. Claims 36, 37, and 42 to 70 have been cancelled. Claims 71 to 111 have been added. Claims 1, 8, 13 to 16, 19, 27, 31 to 35, and 38 to 41 have been amended to correct various typographical errors, tradenames, or to better clarify the present invention. Claim 71 replaces Claim 36, and Claim 72 replaces Claim 37. Support for newly added claims 71 to 111 appears in the original claims, the working examples, or in the specification on as shown in the table below. No new matter is believed added. A fee calculation sheet accompanies this response for the newly added claims.

Support for the amendment of pregelatinized starch for Starch 1500 (a synonym); copovidone for Kollidon VA64; polyethylene oxide for PolyOx, etc., lies in the specification or in the Handbook of Pharmaceutical Excipients, (1986) page 296 (for Starch 1500). No new matter is believed added.

Claim #	Phrase	Specification
73	Lubricant… "10 to about 30%" & surfactant " < 5% w/w"	Claims 1, 3 and 7
74	Eudragit 4135F in an amount of about "50 to 90% w/w"	Claim 2
75	Surfactant list	Claim 18
76 to 80	SDS and < 2% w/w	Claims 5,& 6
81	Lubricant list	Claim 8
82 & 83	Stearyl alcohol, and 10 to about 15% w/w	Claims 9 and 10
84 & 85	DME is a "swellable solid", and "amount of 10 to about 50% w/w"	Claims 11 and 13
86 & 87	DME is HPMC, HPMC phthalate, or HPC "about 5 to 50 % w/w"	Claim 12
88 to 92	DME is 40 to 70%, and particuilar DME combo's	Claims 15, 16, 17 & 19
93 to 95	Processing agent is "talc", and present in an amount of "about 1 to about 5% w/w"	Claims 21 and 22
96 and 97	"absorption enhancer" and list of components	Claims 23 and 24

98	Eudragit 4135F of about "50 to about 90%", stearyl alcohol of "about 10 to about 15% w/w", DME is "HPMC, HPC or Hydroxy alkylcellulose derivative"	Claim 2, 10, page 28, lines 7 to 9
99	"distintegrant"	Page 28, lines 14 to 17, and lines 28 to 30
100	Disintegrant list	Page 28, lines 23 to 27 and claims 14
101, 102 and 103	DME includes a "wicking agent", "wicking agent is lactose", and processing aid is "talc"	Claims 28, 29 and 21
104 & 105	DME includes a "wicking agent", "wicking agent is lactose"	Claims 28 and 29
106 & 107	HPC is about "10 to about 70%", and "40 to about 70%"	Page 28, lines 32 to 34
108, 109, & 110	"wicking agent is lactose", and an "amount of 0 to 10%", and "about 5% w/w".	Claim 29 and page 28, lines 34 and 35
111	Disintegrant present in an amount of about "10 to about 40% w/w"	Page 28, lines 27 and 28

Objection to the Claims

Claim 38 is objected to because of various informalities with respect to the SDS excipient. Applicants appreciate the Examiner notice of a typographical error. Claim 38 has been corrected.

Rejection of Claims under 35 USC §112, second paragraph

Claims 31 to 37 and 39 to 41 are rejected under 35 USC §112, 2nd paragraph as being indefinite for failing to particularly point out and distinctly claim the invention. Applicants respectfully traverse this rejection.

The Examiner has noted that Claims 31 to 37 are not clear with respect to the listed numbers being weight percentages, nor whether a Markush group of composition is being claimed. Applicants have added a header to the table of compositions clearly indicating a % w/w amount and a column to indicate that each box is in fact a separate

composition by designating each with a number. If this does not clarify the issue, the Examiner is requested to contact the undersigned to discuss a suitable presentation.

Claims 39 to 41 are stated to have a preamble which is not in "proper form". While Applicants respectfully disagree that, the claims have been amended to incorporate the Examiners suggested claim language.

In view of these amendments and remarks, reconsideration and withdrawal of the rejection to the claims under 35 USC §112, second paragraph is respectfully requested.

Rejection of Claims under 35 USC §103

Claims 1 to 41 are rejected under 35 §USC 103 as being unpatentable over Hatano et al. (US Patent No. 6,309,666) in view of Lehmann et al. (US Patent No. 5,705,189). Applicants respectfully traverse this rejection.

The Hatano et al. reference is cited by the Examiner as teaching:

> "coated capsule compositions comprising a hard outer shell (See Abstract). Suitable materials for the outer shell include methacrylate co-polymers and acrylic co-polymers (See Column 5, Line 42 to Column 6, Line 23). Each of the components of the capsule, including the hard outer shell, may include various excipients, including binders, disintegrants, lubricants, aggregation-preventing agents, plasticizer, and a surfactant. Excipients include lactose and starch..... Such additives may be added in any amount within the scope of the knowledge of one of ordinary skill in the art (See Column 13, Lines 3-5)."

The Hatano et al. '666 patent teaches use of a different polymers overcoating a capsule shell. One polymer, a low pH one, is used not as an IR coating material, but as a delayed release layer. This effect is achieved by applying to a conventional gelatin or hydroxypropyl methylcellulose shell an inner layer of a low pH copolymer (see Columns 7 & 8, Tables 1 and 2) followed by a top-coat of an enteric polymer, such as those listed in Column 5, lines 60 to 67 and Column 6, lines 1 to 37. The top coat is used to avoid premature dissolution of an inner polymer layer of the low pH copolymer during the gastric phase in which it would be soluble. Suitable top coat or enteric polymers are described in Hatano in Column 5, lines 60 to 67, and column

6, lines 1 to 37). Eudragit L100 or S100 are specific copolymers named, but not Eudragit 4135F.

Hatano et al. can utilize for a top coat polymer one which is pH dependent so that it will dissolve in the more alkaline pH of the small intestine. Eudragit 4135F is considered by the manufacturer to be such a pH dependent copolymer.

Once the capsule shell of Hatano et al. passes into the small intestine, the enteric-layer dissolves (as discussed above) thus exposing the inner low pH soluble film which is swellable and permeable, but is not soluble under these conditions.

A key step the '666 patent is the selection of an appropriate thickness of the low pH soluble coat to control the rate of permeation of water, which will then dissolve an organic acid (acidic substance) contained in the capsule shell itself. The dissolution of the organic acid in turn induces dissolution of the low soluble pH polymer layer and pulse-release of the contents of the capsule. The acidic substance can be the active agent as well.

Hatano et al. utilizes the enteric coat polymer in a conventional manner to protect the contents of the capsule from dissolution in the stomach (see Column 6, lines 45 to 58).

The present invention, in contrast to the disclosure of Hatano et al. utilizes a particular enteric coating polymer in a pharmaceutically acceptable composition for injection molding of components. It is not being used as a coating agent on a tablet or capsule shell but as an integral part of the molded components structural wall. More importantly, Applicants have found that the 4135F copolymer composition, as claimed, is not a pH dependent release system, but a pH independent release system. In other words it is time dependent, not pH dependent.

The Examiner has commented on the additional additives mentioned in the Hatano et al. patent and the statement that "Such additives may be added in any amount within the scope of the knowledge of one of ordinary skill in the art (See Column 13, Lines 3-5)." First, the art involved in Hatano et al. relative to Applicants invention, is a coating art, not molded articles. Also, the general statement above goes back to the discussion appearing in Column 11, lines 52 to 62 in which all the separate layers of the Hatano et al. disclosure are lumped together for discussion:

"To each of the contents of the hard capsule, the sealing means, the low pH-soluble polymer film, the enteric coating filming, and the intermediate layer between the low pH-soluble polymer film and the enteric coating film, if necessary, there can be added various additives generally used in the art of pharmaceutical preparation, for instance, an excipient, a binder.....and the like."

The grouping of additional additives described thereafter is not distinguished for use in which of the contents above one [of ordinary skill in the art] might use them in. In general, the contents of the hard capsule being composed of an active agent the agent would normally have a large number of these additives added to help in its dissolution and absorption into the body from the hard capsule shell.

There is no teaching or suggestion in the Hatano et al. patent that the enteric coating polymers, as used therein, would be modified by Applicants specific additives, nor that those additives are used in the same percentages or combinations as claimed herein.

The Lehmann et al. '189 patent is cited by the Examiner for disclosing "processes for producing acrylic and/or methacrylic articles, such as capsules, by molding (see Column 2, Line 53 to Column 3, Line 32)."

The Examiner also states that:

"One of ordinary skill in the art would be motivated to combine the disclosures of Hatano et al. and Lehman et al., in order to produce, with a reasonable expectation of success, a molded capsule shell possessing certain desired characteristics, as imparted by the excipients disclosed by the prior art, it is the position of the examiner that the particular selection of a specific component out of a broader class of excipients is not patentable without a showing by the applicant of its criticality. Although specific weight percentages of each component are not explicitly disclosed by the prior art, the examiner does not find the applicant's claims patentable absent a showing by the applicant of its criticality. Where the general condition of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. .... Thus, the instantly claimed invention is *prima facie* obvious".

The Lehmann et al. patent discloses various compositions of *anionic* methracylates. The coatings are suitable for production of "drug coatings which are soluble in intestinal juices, such as tablet coatings, dies, films, capsules, or multipart dosage units." (see Abstract).

As noted in Applicants specification, page 23, lines 26 to 35, the polymer 4135F is disclosed in the '189 patent as the ratio of components of the E2 emulsion, column 6 line 10 [65:25:10]. The E2 and the E3 emulsions as disclosed by Lehmann do not fit within their claimed compositions as a thermoplastic material, nor are they specifically described as being suitable for molded.

The polymer Eudragit 4135F is not soluble in 0.1N HCl fluid, such as in simulated gastric fluid (SGF), but will be soluble at a higher pH, such as a pH of 7.5, i.e., simulated intestinal fluids (SIF). The unblended polymer is therefore functioning as a pH dependent polymer.

The thermostability, melt flow characteristics, and apparent shear viscosity of the compositions as described in the '189 patent differ within themselves and from the polymer 4135F, see for instance Examples 1, and 7 to 9 as well as Figures 1 and 2.

The resulting physical strength of post-molded components, i.e. their brittleness and tensile strength is a consequence of the composition utilized. How, for instance, will the capsule components be joined together? The molded components of the '189 patent are joined by using a cyano adhesive, see column 5, lines 38-41. Cyano adhesives are not considered a pharmaceutically acceptable adhesive for oral use. While various pharmaceutically acceptable adhesives are contemplated for use with the molded components of the present invention, alternative options such as welding are also considered, see page 9, lines 3 to 36. Not enough information is given in the '189 patent to determine whether their molded compositions will be flexible enough or have sufficient physical strength to undergo such a joining via this method.

Lehmann teaches that the compositions of anionic copolymers can be molded with sole incorporation of a lubricant, or mold releasing agent, such as Glycerol monostearate (GMS) or stearic acid (Column 3, line 67, and Column 4, lines 1 and 2). The Examples disclose incorporation of GMS in amounts ranging from 1 to 6% w/w. Additional excipients can also be added, see Column 3, lines 62 to 67, and Column 4, lines 1 and 2.

The '189 Lehmann patent does not specifically disclose use of stearyl alcohol, talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica or combinations thereof as alternative lubricants. Claims 9, and 10 specifically require use of stearyl alcohol as a lubricant.

The '189 Lehmann patent does not disclose use of surfactants in their compositions, as disclosed in Applicants specification on page 26, lines 15 to 37, and page 27, lines 1 to 3, and as claimed in Claims 3, 4, 5, 6, and 18 to 21.

The present invention requires (see Claim 1) addition of a dissolution modifying excipient (DME) present in amounts of 2.5 to 70% by weight. DME's are described in Applicants specification on page 27, lines 25 to 35 and page 28, lines 1 to 34. In contrast, the '189 patent does not disclose use of a DME in their compositions. Claims 11 to 13 require DME's which are swellable solids, such as HPMC, or HPC. Claims 14 and 15 include non-reducing sugars, water soluble fillers and disintegrants. Claims 16 and 17 are directed to various combinations of these agents.

In particular, there is no suggestion in the '189 patent to incorporate a "super disintegrant" such as croscarmellose sodium, copovidone, or sodium starch glycollate. Super disintegrants are typically utilized in the pharmaceutical industry for compressed tablet formulations (to aid in dissolution), not in the structural wall of a molded capsule shell.

The filler disclosed in Lehmann as an additional excipient is probably glass, or titanium dioxide, or even talc. It is not meant to be a component of the formulation which change the functionality of the polymer.

The composition of the present invention when used in a molded article will provide for a matrix which swells or hydrates at a given rate in any pH media. This effect is not taught or suggested by the disclosure of the '189 patent.

Therefore, the disclosure of Hatano et al. does not direct or motivate the skilled artisan to use the polymer 4135F as a component contained in the structural wall of a molded article. Hatano does not direct or motivate the skilled artisan to incorporate either the dissolution modifying excipients, or surfactants of Applicants into the enteric coating copolymer.

This failure is not remedied by the disclosure of Lehmann. Lehmann directs the skilled artisan to mold an anionic copolymer solely with a lubricant. This alone, has been found by Applicants to be unsuitable for the 4135F emulsion for injection molding. Therefore, neither the Hatano, or the Lehmann patent taken alone or together teach Applicants claimed compositions herein. Therefore, without the necessary motivation, found lacking in the Hatano or Lehmann patents to achieve Applicants claimed invention, a prima facie case of obviousness has not been made by the Examiner.

In view of these remarks, reconsideration and withdrawal of the rejection under 35 USC §103 to Claims 1 to 41 is respectfully requested.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. It is not believed that this paper should cause any additional fees or charges to be required, other than expressly provided for already. However, if this is not the case the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,

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